REMARKS

Claims 40, 42, 44, 46, 56-58, and 61-61 are presently pending. The Examiner has kindly withdrawn several rejections asserted in the previous Office Action. The Examiner, however, has made other rejections and we list them here in the order in which they are addressed.

I. Rejections Under 35 USC § 112

A. Claims 40, 42, 44, 46, 50, and 56-58 are rejected under 35 USC § 112 ¶ 1 as allegedly failing to comply with the enablement requirement.

B. Claims 40, 42, 44, 46, 56-58, and 60-61 are rejected under 35 USC § 112 ¶ 1 as allegedly failing to comply with the written description requirement.

C. Claims 40, 42, 44, 46, 50, 56-58 are rejected under 35 USC § 112 ¶ 2 as allegedly being indefinite.

II. Rejections Under 35 USC §103(a)

A. Claims 40 and 60-61 are allegedly unpatentable over Butler "Production and Secretion Of Recombinant Human Fibrinogen By the Transgenic Murine Mammary Gland" *Master Of Science Thesis*, Blacksburg, VA, in view of Jorgensen et al., *J Biol Chem* 262:6729-6734 (1987), and further in view of van Cott and Velander *Expert Opinion on Investigational Drugs* 7:1683-1690 (1998).

B. Claims 40, 42, 44, 46, 56 and 58 are allegedly unpatentable over Butler "Production and Secretion Of Recombinant Human Fibrinogen By the Transgenic Murine Mammary Gland" *Master Of Science Thesis*, Blacksburg, VA, in view of Jorgensen et al., *J Biol Chem* 262:6729-6734 (1987), and further in view of Le Bonniec et al., *J Biochem* 266:137796-13803 (1991).

C. Claims 40 and 57 are allegedly unpatentable over Butler "Production and Secretion Of Recombinant Human Fibrinogen By the Transgenic Murine Mammary Gland" *Master Of Science Thesis*, Blacksburg, VA, in view of Jorgensen et al., *J Biol Chem*

262:6729-6734 (1987), and further in view of Seegers et al., *Blood* 5:421-433 (1950).

I The Claims Adhere To 35 U.S.C. § 112

A. The Claims Are Enabled

The Examiner states that:

> ... the specification does not give guidance for an artisan to arrive at recombinant prothrombin-thrombin that have activity yet have different structures. ... the changes listed do not give guidance for an artisan to change 30% of the sequence such that the protein is 70% identical to prothrombin ...

Office Action pg 5-6. The Applicants disagree. Nonetheless, without acquiescing to the Examiner's argument but to further the prosecution, and hereby expressly reserving the right to prosecute the original (or similar) claims, Applicants have amended Claims 40 & 44 to remove the partial identity limitations. Claim 60, therefore, is concomitantly canceled. The presently claimed embodiments now recite an amino acid sequence that is identical to human prothrombin and/or thrombin. These amendments are made not to acquiesce to the Examiner's argument but only to further the Applicants' business interests, better define one embodiment and expedite the prosecution of this application.

The Applicants, therefore, respectfully request that the Examiner withdraw the Enablement rejection.

B. The Specification Complies With The Written Description Requirement

In regards to Claims 40, 42, 44, 46, and 56-58, the Examiner admits that:

> It is noted that the Written Description was incorporated within the Enablement rejection, Office Action, September 19, 2006. It is noted that the Written Description rejection is a separate rejection and thus, the issues at hand of December 29, 2005 are reiterated here.

Office Action, pg 7. The Examiner proceeds to provide an identical rejection basis as discussed above in the Enablement section of the present response. Consequently, the Applicants' rely upon the above claim amendments, thereby making the present Written Description rejection moot.

The Applicants, therefore, respectfully request that the Examiner withdraw the Written Description rejection to Claims 40, 42, 44, 46, and 56-58.

In regards to Claims 60 & 61, the Examiner objects to the Applicants' reference to the Revised Interim Written Description Guidelines Training Materials (RIWDGTM) to show that a protein having an amino acid sequence having "at least 95%" or "100%" identity to a parent polypeptide inherently retains activity by stating that:

> ... Example 14 of the Guidelines ... also indicates that the claimed protein has a particular function [and] ... Applicant's citation of the specification, page 9, lines 3-5, do not indicate any particular activity that is monitored.

Office Action, pg. 9. The Applicants' believe the Examiner is engaging in a strained interpretation of the Guidelines. Further, the Applicants' point out that the Guidelines instruct that a proper analysis should include:

> A review of the full content of the specification ...

RIWDGTM, pg. 53. The Examiner should be aware that the Applicants' specification teaches and enables activity assays for prothrombin. Nonetheless, without acquiescing to the Examiner's argument but to further the prosecution, and hereby expressly reserving the right to prosecute the original (or similar) claims, Applicants have amended Claim 61 to recite that prothrombin activity results in the production of thrombin.[1] *See, Applicants' Specification, pg. 37 ln 16 – pg 39 ln 12. in particular pg 37 ln 29 – pg 38 ln 6.* This amendment is made not to acquiesce to the Examiner's argument but only to further the Applicants' business interests, better define one embodiment and expedite the prosecution of this application.

Further in regards to Claim 61, the Examiner believes that the claim term "at least 100% identical" is unclear. The Applicants disagree and believe that the phrase is consistent with standard claim drafting styles. Nonetheless, without acquiescing to the Examiner's argument but to further the prosecution, and hereby expressly reserving the right to prosecute the original (or similar) claims, Applicants have amended Claim 61 to remove the "at least" limitation. This amendment is made not to acquiesce to the Examiner's argument but only to further the Applicants' business interests, better define one embodiment and expedite the prosecution of this application.

[1] The Examiner is reminded that Claim 60 was canceled above for other reasons.

The Applicants, therefore, respectfully request that the Examiner withdraw the above Written Description rejections to Claims 60 & 61.

III. The Claims Are Not *Prima Facie* Obvious

The legal standard for determining a *prima facia* case of obviousness has recently been reaffirmed as consisting of three elements where:

> ... the scope and content of the prior art are to be determined ... [the] differences between the prior art and the claims at issue are to be ascertained; and the level of ordinary skill in the pertinent art resolved. Against this background the obviousness or nonobviousness of the subject matter is determined.

KSR v. Telflex pg 2, Slip Op. (S. Ct. May 2007)(hereinafter referred to as *Teleflex*). In the present case the Examiner has not fulfilled the burden of addressing any of these elements. Instead, the Examiner has cobbled together unrelated teachings from three references in a strained attempt to form an obviousness rejection. Further, the Examiner has made numerous conclusory statements without providing any articulated reasons having a rational underpinning.[2] The Applicants incorporate by reference the arguments made against this same rejection in the last Office Action response and respectfully request reconsideration by the Examiner.

A. Butler, Jorgensen & Van Cott et al. Do Not Make The Claimed Embodiment Obvious

The Examiner points to Butler and states:

> While Butler teaches making recombinant fibrinogen in milk, Butler teaches that making other plasma-derived proteins would be possible in using transgenic mammals. ... Particularly for the fibrin sealant (FS)- technologies, large amounts of pathogen-free thrombin are desirable ...

[2] *In re Kahn*, 441 F. 3d 977, 988 (CA Fed. 2006) ("[R]ejections on obviousness grounds cannot be sustained by mere conclusory statements; instead, there must be some articulated reasoning with some rational underpinning to support the legal conclusion of obviousness") *cited in Teleflex at pg 14.*.

Office Action pg. 10. The Applicants argue that this statement merely identifies a problem in the art that requires solving. The Examiner, in fact, admits this very fact by stating that Butler does not teach making recombinant human prothrombin in the milk of transgenic mammals.[3] The Applicants' specification has solved the above framed problem. Butler does not, even when referring to one of the Applicants' previous publication:

> Fortunately, recombinant vitamin-K-dependent proteins have been produced at high levels in the milk of transgenic pigs (Velander et al., 1996 ... and thus could serve as a SPF source for recombinant prothrombin.

Butler, pg. 4 [emphasis added]. This is speculation at it's very best, and Butler does not provide any articulated reasoning as how to approach the problem. Consequently, the Examiner has provided a conclusory argument that is not permissible:

> Often, it will be necessary ... to look to interrelated teachings of multiple patents ... in order to determine whether there was an apparent reason to combine the known elements in the fashion claimed by the patent at issue. To facilitate review, this analysis should be made explicit. See, *In re Kahn*, 441 F.3d 977, 988 (CA Fed. 2006) ("[R]ejections on obviousness grounds cannot be sustained by mere conclusory statements; instead, there must be some articulated reasoning with some rational underpinning to support the legal conclusion of obviousness").

KSR v. Teleflex, Slip Op No. 04-1350 (U.S. Supreme Court, April 30, 2007) [emphasis added]. *Teleflex* clearly expects an Examiner to provide an argument based upon scientific facts extracted from the cited references. Neither Butler nor Jorgensen et al. (*infra*) provide any scientific facts regarding the construction of a transgenic pig that secretes prothrombin in milk.

Next, the Examiner points to Jorgensen et al. for teaching an:

> ... expression vector comprising the coding sequence of human prothrombin ... used to express in Chinese Hamster Ovary (CHO) cells ...

Office Action pg 11. The Examiner has presented a cited reference that is limited to *in vitro* cell culture protein expression in an unsuccessful attempt to teach Butler's admitted deficiency of not teaching making recombinant human prothrombin in the milk of a

[3] "While Butler teaches making recombinant fibrinogen in the milk of transgenic mammals, Butler does not teach making recombinant human prothrombin." *Office Action, pg. 11* [emphasis added].

transgenic mammal. Jorgensen et al. does not teach any concepts related to transgenic animals. Therefore, the Examiner's combination of Butler and Jorgensen et al. also fails to teach the making of recombinant human prothrombin in the milk of a transgenic mammal.

Nonetheless, the Examiner simply attempts to join the teachings of Butler and Jorgensen et al. with only a conclusory statement:

> One having ordinary skill in the art would have been motivated to substitute these sequences one for the other because Butler teaches that there is a need in the art ...

Office Action, pg. 11. As pointed out above, Butler provides no guidance and/or evidence (much less data) providing any steps that should be taken to produce a transgenic pig that secretes prothrombin in milk. Further, the Examiner believes that because Butler taught that "human fibrinogen was expressed in large quantities in milk"[4] that this, alone, constitutes a reasonable expectation of success that human prothrombin would also be expressed in large quantities. The Applicants point out that the Examiner has no legal, or scientific, basis for making these conclusory statements.

The Applicants respectfully submit that by making these conclusory statements, the Examiner has not provided any evidence as to why a skilled artisan would make the combination. The Examiner has merely stated what the Examiner believes each reference teaches in isolation from the other reference and then stated that it would be obvious to combine the elements. In order to support the combination, the Examiner has merely relied upon the level of skill in the art. This is not permissible. Such unsupported statements are exactly what the Federal Circuit in *In re Rouffet* 149 F.3d 1350 (Fed. Cir. 1998) sought to prevent. The Federal Circuit stated:

> The Board did not ... explain what specific understanding or technological principal within the knowledge of one of ordinary skill in the art would have suggested the combination. Instead, the Board merely invoked the high level of skill in the art. If such a rote invocation could suffice to supply a motivation to combine, the more sophisticated scientific fields would rarely, if ever, experience a patentable technological advance. Instead, in complex scientific fields, the Board could routinely identify the prior art elements in an application, invoke the lofty level of skill, and rest its case for rejection.

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[4] *Office Action pg. 11.*

In re Rouffet, 149 F.3d 1350, 476 USPQ2d 1453, 1458 (Fed. Cir. 1998)(emphasis added)[5].

Furthermore, Jorgensen et al. does not provide any reasonable expectation of success that the disclosed plasmids are useful at high expression levels:

> When prothrombin expression levels are amplified 10-15 fold, however, only approximately 60% of the secreted prothrombin is sufficiently carboxylated to bind to the conformation-specific antibodies. ... It appears that the γ-carboxylation system has a limited capacity for the amount of substrate which can be efficiently processed over a given period of time; when the rate of substrate synthesis exceeds this limit, the extent of γ-carboxylation is reduced.

Jorgensen et al., pg 6733, lhc. Consequently, Jorgensen et al. provides a clear teaching away to use the disclosed plasmids for high yield expression platforms.

Since Jorgensen et al. teaches away from using the disclosed plasmids for high yield expression systems, the combination with Butler fails. Further, the Van Cott publication does not provide any evidence that the plasmids provided in Jorgensen et al. would be fully carboxylated in a high yield expression system. This deficiency underscores the Examiner's erroneous statement that:

> ...one would have been motivated to use the system taught by Butler because there is a higher yield of prothrombin in milk (5 g/liter) than in a mammalian cell expression system (0.55 ug/ml).

Office Action pg 12 [emphasis added]. This is contradictory to the Examiner's previous statement regarding Butler's teachings:

> Transgenic founder animals were identified and recombinant fibrinogen was identified in the milk of the transgenic animals. In one case, one ewe produced about 5g/liter of recombinant protein (Butler, page 8, under "Expression of rhfib in transgenic mice and sheep").

Office Action pg 10 [emphasis added]. The Examiner has improperly substituted "prothrombin" for "fibrinogen" when discussing Butler. The Examiner has admitted that Butler did not produce recombinant prothrombin. (*supra*). The Examiner cannot combine the teachings of Van Cott and Jorgensen with Butler because fibrinogen is not γ-

[5] *In re Rouffet* is not disturbed by *Teleflex* and is relied upon in *In re Kahn* which the *Teleflex* decision treats positively (*supra*).

carboxylated. Therefore, the Examiner's prediction that Butler could produce 5 g/l of "prothrombin" because one ewe produced 5 g/l of "fibrinogen" is completely unsupportable.

The Applicants, therefore, respectfully request that the Examiner withdraw Butler, Jorgensen et al. and Van Cott as references for obviousness against Claims 40, 60, and 61.

B. Butler, Jorgensen & Le Bonniec et al. Do Not Make The Claimed Embodiment Obvious

The Examiner states that:

> As indicated above, given the teaching of Butler, in view of Jorgensen et al., an artisan would have arrived at human prothrombin secreted in milk.

Office Action, pg. 12. The Applicants disagree and hereby reiterate and incorporate by reference the above arguments demonstrating that Butler and Jorgensen et al. fail to create the Applicants' claimed embodiments.

The Examiner introduces Le Bonniec et al. as a reference to teach that prothrombin is post-translationally modified by proteolytic processing. However, Le Bonniec et al. provides no information sufficient to fulfill the above identified deficiencies of Butler and Jorgensen et al. to the Applicants' independent claims. Consequently, since Butler and Jorgensen et al. fail as a proper combination, the teachings of Le Bonniec et al. to a dependent claim are irrelevant.

The Applicants, therefore, respectfully request that the Examiner withdraw Butler, Jorgensen et al. and Le Bonniec et al. as references for obviousness against Claims 40, 42, 44, 46, 56, and 58.

C. Butler, Jorgensen & Seegers et al. Do Not Make The Claimed Embodiment Obvious

The Examiner states that:

> As indicated above, given the teaching of Butler, in view of Jorgensen et al., an artisan would have arrived at human prothrombin secreted in milk.

Office Action, pg. 12. The Applicants disagree and hereby reiterate and incorporate by reference the above arguments demonstrating that Butler and Jorgensen et al. fail to create the Applicants' claimed embodiments.

The Examiner introduces Seegers et al. as a reference to teach that prothrombin is post-translationally modified by proteolytic processing. However, Seegers et al. provides no information sufficient to fulfill the above identified deficiencies of Butler and Jorgensen et al. to the Applicants' independent claims. Consequently, since Butler and Jorgensen et al. fail as a proper combination, the teachings of Seegers et al. to a dependent claim are irrelevant.

The Applicants, therefore, respectfully request that the Examiner withdraw Butler, Jorgensen et al. and Seegers et al. as references for obviousness against Claims 40 & 57.

CONCLUSION

The Applicants believe that the arguments and claim amendments set forth above traverse the Examiner's rejections and, therefore, request that all grounds for rejection be withdrawn for the reasons set above. Should the Examiner believe that a telephone interview would aid in the prosecution of this application, the Applicants encourage the Examiner to call the undersigned collect at 617.984.0616.

Dated: July 16, 2007

By: 

Thomas C. Howerton
Reg. No. 48,650

Medlen & Carroll, LLP
101 Howard Street, Ste. 350
San Francisco, CA 94105
617-984-0616